UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/228,639	01/12/1999	SUSAN LOUISE WESTON	07164.0008	8318

22852 7590 03/12/2002

FINNEGAN, HENDERSON, FARABOW, GARRETT &
DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20005

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/228,639	Applicant(s) WESTON ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed January 22, 2002. Currently, claims 1-3, 5, 12-18 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action contains new grounds of rejection.

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

The list may be found beginning on page 7 of the specification.

Response to Arguments and Declaration

The declaration under 37 CFR 1.132 filed January 22, 2002 is insufficient to overcome the rejection of claims 1-3, 5, 12-18 based upon 103 as set forth in the last Office action. The declaration and exhibits do not clearly explain which facts or data applicant is relying upon. As provided by the MPEP, ""[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." Ex

parte Ishizaka, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992). The declaration by Dr. Gary Brown asserts that Susie Weston's laboratory reports show that certain primers were prone to non-specific priming which makes primers unacceptable for use in this assay (paragraph 5 of Declaration). The exhibits of the laboratory reports however do not appear to identify primers by either sequence or by SEQ ID NO: as relied upon in the instant specification. The exhibits are general to primers designated by mutation name and do not provide any information as to the structure of the primers which fail. Therefore, it is unclear whether these primers which failed are the primers claimed or whether they are within the scope of the claims or whether they constitute unexpected results. Further, the declaration asserts that primer length affedcted the results of the assay (paragraph 6 of Declaration). As explained above, while the declaration asserts primers of different lengths were used, it is not clear from the manual or from the declaration which of these lengths was ideal and whether this result is within the scope of the claims.

As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive and no evidence has been presented that the primer selection performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. Generally, differences in concentration or

temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

Moreover, as provided in MPEP 716.02 (d), unexpected results must be in commensurate scope with the claims. "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)." In the event that the primers of the declaration directed to specific sequences, constitute unexpected results, the claims are broadly drawn to comprising primers of SEQ ID NO:. Therefore, the claims would not been commensurate in scope with the unexpected results.

The declaration is asserting that the teachings of Schumm, focusing on STR loci, is different from mutations in the CFTR gene. It is noted that the examiner was relying upon Schumm to illustrate the multiplexing of eight pairs of primers had been successfully completed. Whether the primers are directed to mutations or STR loci does not take away from the teachings that either pairs of primers may be multiplexed. The primers hybridize to regions flanking the site of interest and the amplify the region of interest. What the region of interest is not the important feature of multiplexing.

MPEP 716.04 discusses the criteria for establishing a long felt need, stating that "Establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt

need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art...Second, the long-felt need must not have been satisfied by another before the invention by applicant...Third, the invention must in fact satisfy the long-felt need." In the instant case, the need in this case would be the ability to identify mutations within the CFTR gene. This need was being met by other methods in the prior art, for example by the methods taught in Little. Thus, the method of the instant invention is not meeting a long felt need, it would simply an improvement of an art recognized method.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A2) Claims 1-2 are indefinite over the recitation "such that each diagnostic primer" because "each diagnostic primer" lacks proper antecedent basis. The claim is not directed to diagnostic primers. The claim refers to primer sets.

B2) Claim 2 is indefinite because it is unclear how the claim limits Claim 1. Claim 1 does not contain amplification primers. Claim 1 does not provide how

amplification primers are different from diagnostic primers and how these fit into the claimed method. Thus, the metes and bounds of the claimed invention are unclear.

C2) Claims 3, 5 are indefinite because it is unclear whether the sets are limited to primers for each of the following mutations or may encompass any additional primers. The claim has been broadly interpreted because Claim 16 allows for additional control primers. Furthermore, it is unclear which of the following alleles the primers are directed for because each mutation designation contains the alernative alleles. It is unclear whether the primers are both normal and mutant or just one of the alleles for each mutation.

D2) Claims 16-18 are indefinite because the claims are directed to set of primers as claims in Claims 1-2. Claims 1-2, however, are directed to method claims. Therefore, the claim improperly depends upon Claims 1-2 as set of primer claims. This rejection may be easily overcome to delete "Claims 1 and 2".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 3, 5 are rejected under 35 U.S.C. 102(e) as being anticipated by Shuber (5,834,181, November 1998).

This rejection is applied based upon the broad claim language. The claim is directed to a set of allele specific primers for each of the following gene mutations. The ASO oligonucleotides provided in Shuber may function as primers. They are specific to certain alleles. Since the specification fails to provide any limiting definition to allele specific primers, the ASO oligonucleotides of Shuber anticipate the claimed invention.

Shuber teaches a set of ASO oligonucleotides representing known cystic fibrosis mutations. Oligonucleotides for each of the claimed mutations has been provided in Col 18 and 19.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claim 17 is rejected under 35 U.S.C. 103(a) as being obvious over Shuber (5,834,181, November 1998) in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995).

This rejection is applied based upon the broad claim language. The claim is directed to a set of allele specific primers for each of the following gene mutations. The ASO oligonucleotides provided in Shuber may function as primers. They are specific to certain alleles. Since the specification fails to provide any limiting definition to allele specific primers, the ASO oligonucleotides of Shuber anticipate the claimed invention.

Shuber teaches a set of ASO oligonucleotides representing known cystic fibrosis mutations. Oligonucleotides for each of the claimed mutations has been provided in Col 18 and 19.

Shuber does not specifically teach packaging the ASO probes of Col 18-19 into a kit.

However, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already comes prepared.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Shuber with the teachings of Ahern to incorporate the necessary reagents into a packaged kit. The ordinary artisan would have been motivated to have packaged the ASO primers, probes, and reagents of Shuber into a kit, as taught by Ahern for the express purpose of saving time and money.

8. Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al (EPO 497527A1, August 5, 1992) and Ferrie et al (Am. J. Human Genetic, Vol. 51, pg. 251-262, 1992) and Newton in view of CFGAC (Cystic Fibrosis Genetic Analysis Consortium, Human Mutation, Vol 4, pg. 167-177, 1994).

This rejection is directed to method claims for detecting the 12 specific mutations.

Little et al. (herein referred to as Little) teaches a method for detecting single nucleotide variations in the cystic fibrosis gene by amplification refractory mutation system (ARMS). The ARMS method includes treating the sample with nucleoside

triphosphates, an agent for polymerization and a diagnostic primer. Moreover, Little teaches that ARMS is able to selectively amplify multiple sites to obtain multiple amplification products to be distinguished simply, accurately, and with minimal operator skill thus providing a robust technique for screening a single sample for multiple nucleotide variations (pg. 2, lines 47-50). Little teaches numerous primers for ARMS analysis of the cystic fibrosis gene (pg. 27-29). Primers for 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H mutations are provided. The instant primers of SEQ ID NO: 12, 16, 17, 18 are identical to the Little primers 1879, 1880, 1879, 2072, respectively. Little teaches an ARMS reaction in which G542X, F508(M), 621+1 G>A, G551D mutations are multiplexed and analyzed.

Ferrie et al. (herein referred to as Ferrie) teaches the development of a multiplex ARMS test for common mutations in the CFTR gene. Ferrie teaches that ARMS systems have numerous advantages over other PCR-based systems including rapid, reliable, nonisotopic, and easily obtained results (pg. 251-252). Ferrie teaches that in principle, ARMS tests can be developed for any mutation. Ferrie teaches that ARMS tests have been developed for the following CFTR mutations: 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H. Moreover, Ferrie teaches how to increase sensitivity and design an ARMS system which would provide the ordinary artisan with the tools needed to optimize a reaction for a specific need. Ferrie teaches altering the primer sequence has a large effect on the yield and specificity of an individuals reaction within the multiplex, while small changes were obtained by altering the primer concentrations (pg. 258, col. 1). Further, Ferrie teaches

that the yield of the primer pair was affected by the rate of hybridization of ARMS primer to the target DNA and the rate at which the bases at the 3' end of the AMRS primer form a suitable substrate for Taq DNA polymerases (pg. 259, col. 2). Modification of the 3' sequence can change the specificity without significantly altering the calculated melting temperature (pg. 259, col. 2). Specificity may also be obtained by additional stabilization in which the choice of mismatched based was determined experimentally, given that purine/purine mismatches or pyrimidine/pyrimidine mismatches showed greater destabilization (pg. 259, col. 2). Also, specificity may be obtained by reducing the primer concentration and inclusion of control PCR reactions (pg. 259, col. 2). Ferrie also cites other references which discuss improving specificity by reducing the concentration of dNTP in the reaction (pg. 259, col. 2). Long primers (30 mers) ensured false priming events were minimized and that primer template interactions were stabilized and minimizing the disruptive effect of DNA polymorphisms (pg. 260, col. 1). Yields of the reaction needed to be relatively similar. Finally, ARMS multiplex has proved extremely reliable and has made the greatest impact on the speed of delivery of results (pg. 260, col. 2).

Newton teaches analyzing mutations in DNA using the amplification refractory mutation system (ARMS). Newton teaches the system is simple, reliable, and non-isotopic and will distinguish between alleles (abstract). Newton teaches how to design the allele specific primers immediately adjacent to the mutation and even teaches that additional deliberate mismatches near the 3' end are appropriate.

However, Estivill et al. (herein referred to as Estivill) teaches geographic distribution and regional origin of 272 cystic fibrosis mutations in European populations. There mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. G542X, W1282X, N1303K, F508(M), G551D are taught to be the most common mutations. Furthermore, all of 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations are common in more than one region (Table 2 and 3).

Furthermore, CGFAC teaches that 24 of the most common mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. The specific frequencies in which these mutations are found are provided.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Little, Ferrie and Newton in view of Estivill and CGFAC to obtain the claimed method as a whole. Little teaches primers for ARMS reactions to determine mutations in the CTFR gene. Ferrie teaches the modifications needed to be made to perform ARMS multiplex analysis. Little teaches numerous primers for ARMS reactions to determine mutations in the CTFR gene, for each of the claimed mutations except 3849+10kb C>T, R1162 and R334. The ordinary artisan would have been able to have performed routine experimentation to optimize the ARMS systems desired for the particular situation. All of the claimed mutations were known at the time the invention were made, as

exemplified by Estivill and CFGAC. With respect to primers for these mutation, designing ARMS primers to these known primers would have been obvious to the ordinary artisan, as taught by Newton. Further Estivill and CFGAC taught the relative frequencies of the mutations in numerous populations. Thus, the ordinary artisan would have been motivated to either have selected certain mutations to screen for which were more probable in the specific individual being studied. Or, the ordinary artisan would have been motivated to screen for a more generic set of mutations which were relatively probable in all different populations based upon the teachings of Little and Ferrie in view of Estivill and CFGAC.

The ordinary artisan would have been motivated to determine whether the mutation was present in a sample using the multiplex ARMS method of Ferrie since the ARMS method is rapid, reliable and nonisotopic. The ordinary artisan would have further been motivated to have optimized primer selection to obtain optimal results for the ARMS reaction, based upon the teachings of Ferrie. Optimizing conditions for the multiplex reaction are taught by Ferrie. Therefore, the ordinary artisan would have been able to optimize the teachings in the art to generate a method which analyzes the 12 mutations claimed. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive. Since the claim is not drawn to any specific sequence, and the art teaches numerous ARMS primers for the cystic fibrosis gene, optimizing conditions to obtain a system of multiplexing would have been routine.

Since Estivill and CFGAC provides the frequencies of CFTR mutations, Ferrie teaches the ordinary artisan how to optimize multiplex ARMS reactions, and Little teaches ARMS reactions are appropriate for determining single mutations in the CFTR, it would have been obvious to have designed a multiplex reaction which suited the individual needs of the artisan as all such modification would have produced functional equivalent results based upon the teachings of Little and Ferrie. Therefore, the generic multiplexing reaction of 12 well known mutations in a well known gene which causes cystic fibrosis would have been obvious.

9. Claims 3, 5 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al (EPO 497527A1, August 5, 1992) and Ferrie et al (Am. J. Human Genetic, Vol. 51, pg. 251-262, 1992) in view of Estivill et al (Human Mutation, Vol. 10, pg. 135-154, 1997) and CFGAC (Cystic Fibrosis Genetic Analysis Consortium, Human Mutation, Vol 4, pg. 167-177, 1994).

This rejection is directed to the generic sets of primers which do not rely upon specific SEQ ID NO:s.

Little et al. (herein referred to as Little) teaches numerous primers for ARMS analysis of the cystic fibrosis gene (pg. 27-29). Primers for 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H mutations are provided. The instant primers of SEQ ID NO: 12, 16, 17, 18 are identical to the Little primers 1879, 1880, 1879, 2072, respectively. Little teaches placing the primers into a kit.

Newton teaches analyzing mutations in DNA using the amplification refractory mutation system (ARMS). Newton teaches the system is simple, reliable, and non-isotopic and will distinguish between alleles (abstract). Newton teaches how to design the allele specific primers immediately adjacent to the mutation and even teaches that additional deliberate mismatches near the 3' end are appropriate.

CGFAC teaches that 24 of the most common mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. The specific frequencies in which these mutations are found are provided.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Little and Newton in view of CGFAC to obtain the invention as a whole. Little teaches numerous primers for ARMS reactions to determine mutations in the CTFR gene, for each of the claimed mutations except 3849+10kb C>T, R1162 and R334. With respect to primers for these mutation, these mutations were well known and studied mutations. Designing ARMS primers to these known primers would have been obvious to the ordinary artisan, as taught by Newton. Designing a set of primers of ARMS primers to known mutations with frequencies taught by CFGAC would have been obvious. Since the sequence of the CFTR gene was known, mutations within the CFTR were known, as taught by CFGAC, generating primers for these regions would have been obvious over the teachings of Little and Newton which teach the properties of the primers needed for the ARMS assay. The ordinary artisan would have been motivated to have used designed

a set of primers for the most frequent mutations as provided by CFGAC. Packaging the primers to these well known and studied mutations into a set would have been obvious for the benefit of marketing. The ordinary artisan would have been motivated to determine whether the mutation was present in a sample since the ARMS method is rapid, reliable and nonisotopic.

With respect to Claim 17, the ordinary artisan would have incorporated the set of primers into a kit. Little teaches packaging the ARMS primers in a kit.

10. Claims 12, 13, 14, 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al (EPO 497527A1, August 5, 1992) and Ferrie et al (Am. J. Human Genetic, Vol. 51, pg. 251-262, 1992) in view of Estivill et al (Human Mutation, Vol. 10, pg. 135-154, 1997) and CFGAC (Cystic Fibrosis Genetic Analysis Consortium, Human Mutation, Vol 4, pg. 167-177, 1994)

This rejection is directed to the claims which require primers comprising specific SEQ ID NO:s.

Little et al. (herein referred to as Little) teaches a method for detecting single nucleotide variations in the cystic fibrosis gene by amplification refractory mutation system (ARMS). The ARMS method includes treating the sample with nucleoside triphosphates, an agent for polymerization and a diagnostic primer. Moreover, Little teaches that ARMS is able to selectively amplify multiple sites to obtain multiple amplification products to be distinguished simply, accurately, and with minimal operator skill thus providing a robust technique for screening a single sample for multiple nucleotide variations (pg. 2, lines 47-50). Little teaches numerous primers for ARMS

analysis of the cystic fibrosis gene (pg. 27-29). Primers for 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H mutations are provided. The instant primers of SEQ ID NO: 12, 16, 17, 18 are identical to the Little primers 1879, 1880, 1879, 2072, respectively. Little teaches an ARMS reaction in which G542X, F508(M), 621+1 G>A, G551D mutations are multiplexed and analyzed. Little teaches placing the primers and reagents for the method in a kit.

Ferrie et al. (herein referred to as Ferrie) teaches the development of a multiplex ARMS test for common mutations in the CFTR gene. Ferrie teaches that ARMS systems have numerous advantages over other PCR-based systems including rapid, reliable, nonisotopic, and easily obtained results (pg. 251-252). Ferrie teaches that in principle, ARMS tests can be developed for any mutation. Ferrie teaches that ARMS tests have been developed for the following CFTR mutations: 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H. Moreover, Ferrie teaches how to increase sensitivity and design an ARMS system which would provide the ordinary artisan with the tools needed to optimize a reaction for a specific need. Ferrie teaches altering the primer sequence has a large effect on the yield and specificity of an individuals reaction within the multiplex, while small changes were obtained by altering the primer concentrations (pg. 258, col. 1). Further, Ferrie teaches that the yield of the primer pair was affected by the rate of hybridization of ARMS primer to the target DNA and the rate at which the bases at the 3' end of the AMRS primer form a suitable substrate for Taq DNA polymerases (pg. 259, col. 2). Modification of the 3' sequence can change the specificity without significantly altering the calculated

melting temperature (pg. 259, col. 2). Specificity may also be obtained by additional stabilization in which the choice of mismatched based was determined experimentally, given that purine/purine mismatches or pyrimidine/pyrimidine mismatches showed greater destabilization (pg. 259, col. 2). Also, specificity may be obtained by reducing the primer concentration and inclusion of control PCR reactions (pg. 259, col. 2). Ferrie also cites other references which discuss improving specificity by reducing the concentration of dNTP in the reaction (pg. 259, col. 2). Long primers (30 mers) ensured false priming events were minimized and that primer template interactions were stabilized and minimizing the disruptive effect of DNA polymorphisms (pg. 260, col. 1). Yields of the reaction needed to be relatively similar. Finally, ARMS multiplex has proved extremely reliable and has made the greatest impact on the speed of delivery of results (pg. 260, col. 2).

Newton teaches analyzing mutations in DNA using the amplification refractory mutation system (ARMS). Newton teaches the system is simple, reliable, and non-isotopic and will distinguish between alleles (abstract). Newton teaches how to design the allele specific primers immediately adjacent to the mutation and even teaches that additional deliberate mismatches near the 3' end are appropriate. Newton teaches control primers to the apolipoprotein B gene.

Estivill et al. (herein referred to as Estivill) teaches geographic distribution and regional origin of 272 cystic fibrosis mutations in European populations. There mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. G542X, W1282X,

N1303K, F508(M), G551D are taught to be the most common mutations. Furthermore, all of 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations are common in more than one region (Table 2 and 3).

Furthermore, CGFAC teaches that 24 of the most common mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. The specific frequencies in which these mutations are found are provided.

Neither Little, Ferrie, Newton, Estivill, nor CGFAC specifically teach SEQ ID NO: 5, 7, 8, 10, 14

Therefore, it would have been **prima facie** obvious, given all of the teachings in the art, to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Little, Ferrie and Newton in view of Estivill and CGFAC to obtain the claimed method as a whole. Little teaches primers for ARMS reactions to determine mutations in the CTFR gene. Ferrie teaches the modifications needed to be made to perform ARMS multiplex analysis. Little teaches numerous primers for ARMS reactions to determine mutations in the CTFR gene, for each of the claimed mutations except 3849+10kb C>T, R1162 and R334. The ordinary artisan would have been able to have performed routine experimentation to optimize the ARMS systems desired for the particular situation. All of the claimed mutations were known at the time the invention were made, as exemplified by Estivill and CFGAC. With respect to primers for these mutation, designing ARMS primers to these known primers would have been

obvious to the ordinary artisan, as taught by Newton. Further Estivill and CFGAC taught the relative frequencies of the mutations in numerous populations. Thus, the ordinary artisan would have been motivated to either have selected certain mutations to screen for which were more probable in the specific individual being studied. Or, the ordinary artisan would have been motivated to screen for a more generic set of mutations which were relatively probable in all different populations based upon the teachings of Little and Ferrie in view of Estivill and CFGAC.

The ordinary artisan would have been motivated to determine whether the mutation was present in a sample using the multiplex ARMS method of Ferrie since the ARMS method is rapid, reliable and nonisotopic. The ordinary artisan would have further been motivated to have optimized primer selection to obtain optimal results for the ARMS reaction, based upon the teachings of Ferrie. Optimizing conditions for the multiplex reaction are taught by Ferrie. Therefore, the ordinary artisan would have been able to optimize the teachings in the art to generate a method which analyzes the 12 mutations claimed. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Routine optimization is not considered inventive.

The ordinary artisan would have optimized primer selection to obtain optimal results for the ARMS reaction, based upon the teachings of optimization by Ferrie. Further, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA

does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the primers taught by Little, Ferrie and Newton in view of the known CFTR gene, a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited reference in the absence of secondary considerations. The instant primers are designed to be ARMS primers (or allele specific primers). As taught by Netwon these primers have distinct characteristics which require the primers to be immediately adjacent to the mutation. Thus, since the known primers have a specific location within the known CFTR gene, designing of ARMS primers would be directed to a specific location of the gene, rather than anywhere on the gene.

With respect to Claim 16 and 18 directed to sets of primers and kits comprising control primers, Newton teaches control primers directed to apolipoprotein B gene which encompass the instant SEQ ID NO: 1 and overlap SEQ ID NO: 2. Therefore, modifying control primers to a known region would have been functionally equivalent primers. Claim 16 and 17 with respect to SEQ ID NO: 1 are directed broadly to

comprising primers, therefore, the Control 1 primer of Newton falls within the scope of the Claim.

With respect to Claim 17, the ordinary artisan would have been motivated to have placed the primers into a kit, as taught by Little. Reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged primers for ARMS multiplex analysis of CFTR in a kit for the expected benefits of convenience and cost-effectiveness of practioners in the art wishing to analyze the CFTR gene.

Since Estivill and CFGAC provides the frequencies of CFTR mutations, Ferrie teaches the ordinary artisan how to optimize multiplex ARMS reactions, and Little teaches ARMS reactions are appropriate for determining single mutations in the CFTR, it would have been obvious to have designed a multiplex reaction which suited the individual needs of the artisan as all such modification would have produced functional equivalent results based upon the teachings of Little and Ferrie. Therefore, the generic multiplexing reaction of 12 well known mutations in a well known gene which causes cystic fibrosis would have been obvious.

Conclusion

11. No claims allowable over the art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
March 6, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600